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**Female human iPSCs retain an inactive X chromosome.**

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**Public Summary:**

X chromosome inactivation refers to the silencing of one of the two X chromosomes in females. Here we studied what happens to the inactive X chromosome during reprogramming to the induced pluripotent stem cell (iPSC) state. We found that reactivation of the inactive X chromosome does not occur in human reprogramming. This is in contrast to reprogramming of mouse cells, where the inactive X reactivates. Furthermore, we showed that female human iPSCs exhibit nonrandom X chromosome inactivation, thus all cells in the population express the same X chromosome. In contrast, differentiated female cells are mosaic for which X chromosome they express. Our finding of nonrandom X chromosome inactivation in female human iPSCs will affect studies of X-linked diseases and the use of female human iPSCs.

**Scientific Abstract:**

Generating induced pluripotent stem cells (iPSCs) requires massive epigenome reorganization. It is unclear whether reprogramming of female human cells reactivates the inactive X chromosome (Xi), as in mouse. Here we establish that human (h)iPSCs derived from several female fibroblasts under standard culture conditions carry an Xi. Despite the lack of reactivation, the Xi undergoes defined chromatin changes, and expansion of hiPSCs can lead to partial loss of XIST RNA. These results indicate that hiPSCs are epigenetically dynamic and do not display a pristine state of X inactivation with two active Xs as found in some female human embryonic stem cell lines. Furthermore, whereas fibroblasts are mosaic for the Xi, hiPSCs are clonal. This nonrandom pattern of X chromosome inactivation in female hiPSCs, which is maintained upon differentiation, has critical implications for clinical applications and disease modeling, and could be exploited for a unique form of gene therapy for X-linked diseases.

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